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III. REMARKS

Preliminary Remarks

Reconsideration and allowance of the present application based on the following remarks are respectfully requested. Claims 1 and 3-24 are currently pending and remain at issue in this application.

Solely to expedite prosecution and without prejudice to the applicants' right to seek broader claims in a continuing application, the applicants have canceled claim 3. Amended claim 4 is directed to the method of claim 1 wherein the intake of the progestogen only preparations or combined oral contraceptive preparations or LHRH antagonist or combinations thereof is completed on Mondays to Thursdays to obtain start of menstrual bleeding and of ovarian stimulation therapy on Fridays to Mondays and oocyte pick up and further ART procedures can be scheduled and undertaken on Mondays to Thursdays. Support for amended claim 4 can be found throughout the specification, for example, on page 3, lines 25-32.

Amended claim 21 is directed to a method of therapeutic management of infertility by programming of controlled ovarian stimulation and assisted reproductive technique procedures according to claim 1 in which the stimulation is performed by administration of urinary FSH or recombinant FSH or HMG or recombinant LH or a combination thereof. Support for amended claim 21 is found throughout the specification, for example, on page 4, line 15-18.

This response is timely filed as it is accompanied by a petition for an extension of time to file in the third month and the requisite fee. The applicants do not intend by these or any amendments to abandon the subject matter of the claims as originally filed or later presented, and reserve the right to pursue such subject matter in continuing applications.

Patentability Remarks

Rejection Pursuant to 35 U.S.C. §112, First Paragraph, Enablement

On pages 2-8 of the official action, the examiner rejected claims 1, 3-5, 11, and 21 under 35 U.S.C. §112, first paragraph, for allegedly lacking enablement. Specifically, the examiner asserted that while the specification was enabling for co-administration of particular and specific LHRH antagonists (such as those recited in claims 5-9), LHRH agonists, or LH with progestogen, the specification does not provide reasonable enablement

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for any substances or compounds represented by the generic terms "LHRH antagonists, LHRH-agonists, or LH" for co-administration with progestogen.

Solely to expedite prosecution and without prejudice to the applicants' right to seek broader claims in a continuing application, the applicants have amended claim 1 and its reference to LHRH antagonists, LH agonist, and luteinizing hormone. Amended claim 1 is now directed to a method for therapeutic management of infertility by programming controlled ovarian stimulation (COS) and assisted reproductive techniques (ART) in order to optimize oocyte harvesting and fertilization, the method comprising the following steps: (a) programming the start of controlled ovarian stimulation via administration of a compound selected from the group consisting of a LHRH antagonists, a progestogen only preparation, a combined oral contraceptive preparation, and a combination thereof wherein the LHRH antagonist is selected from the group consisting of cetrorelix, teverelix, ganirelix, antide, and abavelix and is administered at a dosage range between 0.5 mg to 10 mg during the luteal phase of the menstrual cycle to induce luteolysis, and wherein the progestogen only preparations and/or the combined oral contraception preparations are administered during both the luteal phase and day 1 or 2 of the menstrual cycle; (b) exogenous stimulation of the ovarian follicle growth via administration of a compound selected from the group consisting of urinary FSH, recombinant FSH, HMG, recombinant LH, clomiphene, and a combination thereof; (c) suppression of premature ovulation via administration of a LHRH-antagonist selected from the group consisting of cetrorelix, teverelix, ganirelix, antide, and abavelix during the follicular stage of the menstrual cycle; (d) induce ovulation via administration of HCG; and (e) application of assisted reproduction techniques, especially IVF, ICSI, GIFT, ZIFT or by intrauterine insemination via sperm injection. Support for amended claim 1 can be found throughout the specification, for example, on pages 3, 4, and 5.

The applicants submit that the examiner has acknowledged that the LHRH antagonists' cetrorelix, teverelix, ganirelix, antide, and abavelix are enabled by the specification. [See Official Action on page 2] The applicants also submit that the terms LHRH antagonists, LH agonists and LH were well known in the art by one of ordinary skill in the art at the time of filing for use in the claimed methods. Nevertheless, the applicants submit that amended claim 1 is fully enabled by the specification regarding the specific reference to the urinary and recombinant FSH, HMG, recombinant LH and antiestrogens such as clomiphene for purposes of stimulating the ovaries for development of follicle oocytes. [See page 4, lines 15-18 of the specification]. As discussed above, claim 3 has been canceled

without prejudice. Claims 4, 5, 11, and 21 depend from and contain the same limitations as amended claim 1. Accordingly, the applicants submit that these claims are fully enabled as well. In view of the foregoing amendment and remarks, the applicants respectfully submit that the rejection of claims 1, 3-5, 11, and 21 under 35 U.S.C. §112, first paragraph, for allegedly lacking enablement, has been overcome and should be withdrawn.

Rejection Pursuant to 35 U.S.C. §103(a), Obviousness

On pages 8-14 of the official action, the examiner rejected claims 1 and 3-24 under 35 U.S.C. §103(a) as being unpatentable over Engel *et al.*, EP 0788799 (hereafter Engel), Albano *et al.*, *Human Reproduction* 11:2114-2118 (1996; hereafter Albano), Felberbaum *et al.*, 10th World Congress on *In Vitro Fertilization and Assisted Reproduction* 397-404 (hereafter Felberbaum), and Garfield *et al.*, U.S. Patent No. 5,470,847 (hereafter Garfield) in view of Deghenghi, U.S. Patent No. 5,945,128 (hereafter Deghenghi), Rabasseda *et al.*, Drugs of the Future 24:393-403 (1999; hereafter Rabasseda), and Kent, U.S. Patent No. 4,016,259 (hereafter Kent). Specifically, the examiner alleged that one of ordinary skill would have been motivated to employ the particular LHRH-antagonist such as teverelix, antide, and abarelix since teverelix, antide, and abarelix are known to be LHRH-antagonists used in the method of controlled ovarian stimulation and assisted reproductive techniques according to Engel, Albano, Felberbaum, Deghenghi, and Rabasseda. The examiner further alleged that the results in the instant method on pages 4 and 5 of the specification provide no clear and convincing evidence of non-obviousness or unexpected results over the cited prior art since there is no side by side comparison with the closest prior art. The examiner concluded by stating that since all methods and composition components herein are known to be useful to treat or manage infertility, it is considered prima facie obvious to combine them in a single method useful for the very same purpose.

A *prima facie* case of obviousness requires: (1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) the teaching or suggestion of all the claim limitations of the applicants' invention in the combined prior art references; and (3) a reasonable expectation of success. M.P.E.P. § 2143. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure." *In re Vaeck*, 947 F.2d 488, 20

USPQ2d 1438 (Fed. Cir. 1991). Moreover, the prior art must provide some teaching, suggestion or motivation to make the specific combination that was made by the applicant." *In re Dance*, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) (emphasis added) (citing *In re Raynes*, 7 F.3d 1037, 1039, 28 USPQ2d 1630, 1631 (Fed. Cir. 1993); *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992).

As discussed above, amended claim 1 is directed to a method for therapeutic management of infertility by programming controlled ovarian stimulation (COS) and assisted reproductive techniques (ART) in order to optimize oocyte harvesting and fertilization by (a) programming the start of controlled ovarian stimulation via administration of a compound selected from the group consisting of a LHRH antagonists, a progestogen only preparation, a combined oral contraceptive preparation, and a combination thereof wherein the LHRH antagonist is selected from the group consisting of cetrorelix, teverelix, ganirelix, antide, and abavelix, and is administered at a dosage range between 0.5 mg to 10 mg during the luteal phase of the menstrual cycle to induce luteolysis, and wherein the progestogen only preparations and/or the combined oral contraception preparations are administered during both the luteal phase and day 1 or 2 of the menstrual cycle, (b) exogenous stimulation of the ovarian follicle growth via administration of a compound selected from the group consisting of urinary FSH, recombinant FSH, HMG, recombinant LH, clomiphene, and a combination thereof, (c) suppression of premature ovulation via administration of a LHRH-antagonist selected from the group consisting of cetrorelix, teverelix, ganirelix, antide, and abavelix during the follicular stage of the menstrual cycle, (d) induce ovulation via administration of HCG and (e) application of assisted reproduction techniques, especially IVF, ICSI, GIFT, ZIFT or via intrauterine insemination by sperm injection. In view of the amendment and foregoing remarks, the applicants respectfully traverse the examiner's rejection.

The applicants submit that the disclosure establishes a novel and unobvious method of overcoming infertility by target administration of oral contraceptives or progesterones that control the resetting and beginning of the menstrual cycle for purposes of programming controlled ovarian stimulation and subsequent harvesting and fertilizing the eggs using assisted reproductive techniques. In contrast, the cited publications in this rejection merely focus on preventing ovulation and LH surges, and fail to teach the optimization of programming controlled ovarian stimulation or assisted reproductive techniques.

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The applicants submit that the disclosure also teaches that LHRH antagonists such as cetrorelix, teverelix, ganierelix, antide or abarelix are used in two novel ways. The first way is to use the LHRH antagonists for the purpose of programming the beginning of the menstrual cycle. This is accomplished by using the LHRH antagonist for ending the previous normal menstrual cycle via luteolysis, or a degeneration of the corpus leteum. Once the menstrual cycle is reset, physicians are able to control ovarian stimulation and fertilize eggs using assisted reproductive techniques. Second, the LHRH antagonists are used in preventing premature luteinizing hormone (LH) surge and subsequent unexpected ovulation during the controlled ovarian stimulation and assisted reproductive technique step of the claimed method. Accordingly, the applicants respectfully submit that the novel use of contraceptives such as progestogens (or the combination of progestogens and estradiol) in combination with LHRH antagonists are used to program controlled ovarian stimulation and allows physicians to predict the day in which to perform assisted reproductive techniques to maximize fertilizing an egg. The seven publication presented by the examiner neither teach nor suggest this claimed invention. Each of the references will be discussed and compared to our claimed invention below.

Engel et al., EP 07887799

Engel *et al.*, EP 07887799 (hereafter "Engel"), a primary reference, fails to teach or suggest that (1) oral administration of progestogen preparations (*e.g.*, ethinylestradiol and progestogen) combined with mono-, bi-, and triphasic contraceptive preparations (*e.g.*, mestranol and progestogen) in conjunction with LHRH antagonists selected from the group consisting of cetrorelix, teverelix, ganierelix, antide and abarelix, **can be administered together to reset the menstrual cycle**. Resetting the menstrual cycle allows physicians to **properly program the controlled** ovarian stimulation therapy (COS) and subsequent assisted reproductive techniques (ART). Engel fails to teach or suggest this "programming" step in their teachings.

Engel further fails to disclose the effective dosage range of 0.5 mg to 10 mg of LHRH antagonist that is to be administered (in conjunction with the progestogen or other oral conceptive preparations) **during the luteal phase** for purposes of inducing lueteolysis and more importantly decreasing the levels of progesterone present during this stage of the menstrual cycle. By administering LHRH antagonist (in conjunction with the progestogen or other oral conceptive preparations) during the luteal phase, the applicants were able to

effectively reset the menstrual cycle so that physicians were able to control stimulation of the ovaries and fertilize eggs using assisted reproductive techniques. In the applicants' novel protocol, they also administered LHRH antagonsist during the follicular phase as well. This administration was done a few days prior to ovulation (5 days if using a multiple dose regimen of cetrorelix; 3 days if using a single dose regimen of cetrorelix) to prevent a LH surge.

In contrast, Engel teaches administering LHRH antagonists **only during the follicular phase of the menstrual cycle** in order to prevent premature LH surge. In fact, in Engel, only progesterone is used during the luteal phase **to avoid residual effects** of the LHRH antagonist that was used to prevent a premature LH surge. The applicants teach that LH antagonist can be used in conjunction with oral contraceptives (*i.e.*, progesterone, progesterone + estradiol) during the luteal phase in order to reset the menstrual cycle and program or set a prescribed timeline for control ovarian stimulation (COS) and then a subsequent oocyte pick up and fertilization using assisted reproductive techniques (ART). In summary, Engel fails to teach or suggest to one of skill in the art that each COS/ART prescribed timeline can be controlled by resetting the menstrual cycle during the luteal phase using the combination of oral contraceptives or progestogen only drugs in conjunction with injection of LHRH antagonists.

Albano *et al., Human Reproduction 11:2114-2118 (1996)*

Albano *et al.*, *Human Reproduction* 11:2114-2118 (1996) (hereafter Albano), a primary reference, fail to teach or suggest that (1) oral administration of progestogen preparations (*e.g.*, ethinylestradiol and progestogen) combined with mono-, bi-, and triphasic contraceptive preparations (*e.g.*, mestranol and progestogen) in conjunction with (2) LHRH antagonists selected from the group consisting of cetrorelix, teverelix, ganierelix, antide and abarelix **can be administered together to reset the menstrual cycle**. Thus, Albano fails to teach or suggest the importance of being able to program the menstrual cycle to allow physicians to properly program the controlled ovarian stimulation therapy (COS) and subsequent assisted reproductive techniques (ART). Although Albano reported that progesterone levels are lowered during the follicular phase (it is well known in the art that progesterone levels during the follicular phase are very low) via administrationof LHRH antagonist (used in preventing LH surges), this drop in concentration during the follicular phase does not allow for any conclusions on what would happen if LHRH antagonists was

used during the luteal phase, which is characterized as having very high levels of progesterone. The absolute values of progesterone measured by Albano were very low and the drop in levels was only detected using sensitive methods that are not normally available to one of skill. In many cases, residual LHRH antagonists leftover from treating premature LH surges for a controlled ovulation step **do not prevent the large increase in progesterone levels during the luteal phase**. Therefore, the examiner cannot conclude from the teachings of Albano that LHRH antagonist used for COS/ART procedures is necessarily going to control the level of progesterone during the luteal phase.

In response of this lack of teaching in the art (for example, Albano), the applicants have developed a method wherein LHRH antagonist is administered twice. First, LHRH antagonist is administered during the luteal phase of a menstrual cycle at a concentration between 0.5 mg to 10 mg to decrease the high levels of progesterone and induce luteolysis (**thus resetting the menstrual cycle**). Second, LHRH antagonist is administered to prevent LH surges during the COS/ART procedures of the follicular stage. Accordingly, Albano fails to teach or recognize the importance of administering LHRH antagonist during the luteal phase as well as during the follicular stage. LHRH antagonists are effective at resetting the menstrual cycle during the luteal stage for purposes of effectively programming COS/ART procedures. In summary, like Engel, Albano fails to teach or suggest that each COS/ART prescribed timeline **can be controlled by resetting the menstrual cycle** during the luteal phase using the combination of oral contraceptives or progestogen only drugs in conjunction with the injection of LHRH antagonists.

Felberbaum et al. (10th World Congress on In Vitro Fertilization and Assisted Reproduction, Gomel et al.(Eds.), Moduzzi Editore, Bologna, Italy pgs. 397-404 (1997).

Felberbaum *et al.*, 10th World Congress on In Vitrol Fertilization and Assisted Reproduction (1997; hereafter "Felberbaum"), a primary reference, fail to teach or suggest (1) oral administration of progestogen preparations (e.g., ethinylestradiol and progestogen) combined with mono-, bi-, or triphasic oral contraceptive preparations (e.g., mestranol and progestogen) in conjunction with administration of (2) LHRH antagonists selected from the group consisting of cetrorelix, teverelix, ganierelix, antide or abarelix to reset the menstrual cycle and properly program the controlled ovarian stimulation therapy (COS) and subsequent assisted reproductive techniques (ART). For example, Felberbaum's discussion on the first full paragraph of page 399 does not provide sufficient guidance to one of skill in the art at the time of filing regarding how to exactly go about resetting the menstrual cycle and properly

timing the COS regimen. Although Felberbaum discusses the use of LHRH antagonists for the prevention of LH surges, it does not provide sufficient guidance as to how the injection of HCG (human chorionic gonadotropin) and oocyte pick up **can be properly timed in a clinical setting without timing the start of a new menstrual cycle**. In fact, Felberbaum refers to its control of ovulation during the follicular phases as a balance that must be carried out by ART specialists due to the complex feed-back mechanisms of apply LHRH antagonist in conjunction with HGC.

The discussion of a "fall in gonadotropins followed by a fall of sex steroids" on page 398 of Felberbaum refers to administration of LHRH agonists for woman suffering from endometriosis. This discussion does not specifically relate to LHRH antagonist application in a COS/ART program or during luteal phase to reset the menstrual cycle for purposes of programming a COS/ART program.

In addition, Felberbaum incorrectly characterizes how LHRH antagonists affect FSH levels. On the last paragraph on page 401, the authors of Felberbaum discuss that FSH levels are less profoundly suppressed during LHRH antagonists administration. Yet, during programmed COS/ART cycles, **only LH is suppressed following** the administration of LHRH antagonists while FSH continuously increases during the follicular phase. Thus, Felberbaum does not appear to completely understand how to therapeutically manage program controlled ovarian stimulation and assisted reproductive procedures.

Most importantly, Felberbaum fails to teach or suggest that properly programming controlled ovarian stimulation and oocyte pickup via assisted reproductive techniques **requires properly resetting the menstrual cycle by oral administration of contraceptives or progestrogen containing drugs in conjunction with LHRH antagonists** during the luteal phase of a woman's menstrual cycle. Thus, Felberbaum does not teach one of skill how to reset the menstrual cycle in order to properly time each step of different COS/ART procedures.

Garfield et al., U.S. Patent No. 5,470,847

Garfield *et al.*, U.S. Patent No. 5,470,847 (hereafter "Garfield") teach the inhibition of ovulation by administering an arginine derivative, which acts as a nitric oxide synthase inhibitor, alone or in combination with one or more progestin, an estrogen, and an LHRH antagonist prevents conception. **In stark contrast, the applicants teach using progestrogen-only compounds or in combination of estrogens and progesterone to reset**

a menstrual cycle during the luteal stage and start a new menstrual cycle. The progestrogen only or estrogen/progesterone therapeutic regimen is not used to inhibit LH or the LH surge because this would have deleterious affects on growing follicles/oocytes during ovulation (the follicular stage). In conjunction with these therapeutic treatments (*i.e.*, progesterone, progesterone + estradiol), the applicants teach that LHRH antagonists are used during the luteal phase to reset the menstrual cycle for purposes of programming a COS/ART regimens. **Thus, the applicants' claimed method, in contrast to Garfield, does not have the purpose of preventing conception**. In fact, even if LHRH antagonists were used only a few days during the follicular phase in view of Garfield's teachings and alleged by the examiner, castration and the inability to develop oocytes would occur (including other side effects) due to the other hormones used in Garfield's formulations and protocols (see above).

Most importantly, Garfield does not teach the programming of the start of the menstrual cycle where COS/ART is performed wherein its' timing is critically based upon **administration of the oral contraceptives, progestagen only compounds, and LHRH antagonists (such as cetrorelix, teverelix, antide, and abarelix) regimen during the luteal phase**. In addition, Garfield fails to teach or suggest that ovarian stimulation occurs between Friday and Monday for subsequent oocyte pick up and assisted reproductive techniques undertaken between Monday and Thursday due to the use of oral contraceptives and/or LHRH antagonists to program the COS/ART cycle.

R. Deghenghi, U.S. Patent No. 5,945,128

R. Deghenghi, U.S. Patent No. 5,945,128 (hereafter "Deghenghi"), a secondary reference, does little to overcome the failings of the primary documents (Engel, Albano, Felberbaum, and Garfield). Specifically, Deghenghi does not teach that LHRH antagonists, preferably cetrorelix, and oral contraceptives (*i.e.*, progesterone, progesterone + estradiol) can be administered during the luteal phase of the menstrual cycle for the purpose of resetting the menstrual cycle to properly program COS/ART techniques. Instead Deghenghi only teaches using LHRH antagonists in an implant over a period of one to twelve months for purposes of regulating the levels of testosterone by suppressing LH and FSH. In contrast, the applicants teach that LHRH antagonists suppress LH surges prior to ovulation (along with controlling luteolysis) in one embodiment of the invention. Deghenghi's teaching of using an implant to deliver LHRH antagonist over one month is counter productive to our procedure of using LHRH antagonist for (1) programming COS/ART cycles for purposes of suppressing only

LH in woman prior to ovulation, and (2) resetting the menstrual cycle during the luteal phase. The applicants teach that application of an LHRH antagonist for programming COS/ART takes place only over a few days during the luteal phase of the cycle preceding COS/ART procedures. **The applicants believe that applying the teachings of Deghenghi to their claimed method would have a profound disturbance on the entire hormonal feed back mechanisms and physiology**. Again, Deghenghi teachings of delivering LHRH antagonists for at least a month are counter to the procedure of programming COS/ART cycles using LHRH antagonists along with progesterone or the contraceptive pill for resetting and beginning a new menstruation cycle. In conclusion, the applicants submit that the injection of cetrorelix, teverelix, ganirelix or antide as presented by Deghenghi fails to teach or suggest using this formulation to induce luteolysis and reset the menstrual cycle in order to time each step of the different COS/ART procedures for female oocyte development, harvesting, and fertilization.

Rabasseda et al., Drugs of the Future 24:393-403 (1999)

Rabasseda *et al., Drugs of the Future*, 24:393-403 (1999; hereafter "Rabasseda"), a secondary reference, similarly did little to overcome the failings of the primary documents (Engel, Albano, Felberbaum, and Garfield). Specifically, Rabasseda teaches only that ganirelix can be used to overcome female infertility, but does not provide any guidance to the specific timing for programming COS/ART procedures or preventing LH surges. In addition, Rabasseda fails to teach or suggest using abarelix for treatment of patients with only prostate cancer or endometriosis and not for the purposes of overcoming female infertility. In addition, Rabasseda fails to teach or suggest that the menstrual cycle can be reset for purposes of programming COS/ART procedures by administering oral contraceptives, progestogen only compounds and/or LHRH antagonists during the luteal phase to induce luteolysis. Accordingly, one of skill would not find using ganirelix or abarelix to prevent premature LH surges nor manipulate the start of programming COS/ART procedures by resetting the menstrual cycle through the teachings of the primary document in view of Rabasseda.

Kent, Jr., U.S. Patent No. 4,016,259

Kent, Jr., U.S. Patent No. 4,016,259 (hereafter "Kent"), a secondary reference, also does little to overcome the failing of the primary documents (Engel, Albino, Felberbaum, and

Garfield). Kent only teaches that progestogens can be combined with estrogens to be used as contraceptives and the possible risks associated with their use. Specifically, Kent does not disclose the use of contraceptives (*i.e.*, progestogens or combination of progestogens with estradiol) alone, or in combination with LHRH antagonists for the programming of COS/ART procedures by resetting and timing the onset of a new menstrual cycle by withdrawal of sex hormones. Furthermore, Kent further fails to teach or suggest disclosing a program for ovarian stimulation therapy from Friday to Monday using a combination of cetrorelix to prevent an LH surge and human chorionic gonadotropin to stimulate release of the oocyte. Furthermore, Kent also fails to teach or suggest using assisted reproductive techniques to pick up an oocyte and embryo transfers on the following Monday to Thursday. Finally, Kent fails to discuss the use of LHRH antagonists to induce luteolysis and thus programming of the COS/ART procedures. Accordingly, one of skill in the art would not find using LHRH antagonists to prevent premature LH surges or contraceptive to prevent pregnancy could be used to manipulate the programming of COS/ART cycles (*i.e.*, resetting the start of a menstrual cycle for purposes of timing ART procedures) through the teachings of the primary documents in view of Kent.

Overall Conclusions:

In none of the references discussed above is there a teaching or suggestion to motivate one of skill to optimize the treatment of female infertility by programming the controlled ovarian stimulation protocol and assisted reproductive techniques. This programming is dependent upon the novel discovery that administration of oral contraceptives in the form of progestogens or progestogens with estrodiol can be used to reset the menstrual cycle. In addition, the further administration of LHRH antagonists such as cetrorelix can be used to induce luteolysis during the luteal phase of the menstrual cycle and program the onset of a new menstrual cycle . The timing of these procedures allows for the stimulation of oocytes from a Friday to a Monday, an oocyte pick up and fertilization by ART protocols between Monday and Friday. This predictable, manipulable program which manages overcoming infertility in a woman is neither taught nor disclosed by the seven publications discussed above. None of these references discuss using oral contraceptive preparations or progestogens during controlled ovarian stimulation to control premature LH surges. These references in fact teach against overcoming infertility successfully by using the claimed invention. The combined teaching of the references cited in the official action state that

combining progesterone and LHRH antagonists have deleterious effects on growing follicles and oocytes using COS protocols, and thus inhibiting successful implantation of good quality embryos using ART protocols. Contrary to these teachings, the applicants have described that LHRH antagonist can be used effectively in two stages of the menstrual cycle. LHRH antagonists can be used during the luteal phase to induce luteolysis and reset the menstrual cycle. LHRH antagonist can also be used during the follicular phase either four days (if using multiple dose regimen) or two days (if using a single dose regimen) before ovulation induction by HCG. Accordingly, in view of the foregoing remarks, the applicants believe the claimed invention is not obvious in view of the cited art in the current obviousness rejection.

The applicants further submit four clinical studies (published after the filing date of our application) that verify and discuss the secondary considerations over obviousness regarding the applicants' unexpected success in fertility via programming the COS/ART cycles by resetting the menstrual cycle using either LHRH antagonist, progesterone, progesterone plus oral contraceptives or a combination thereof.

Vlaisavljevic et al., Reproductive BioMedicine Online 7:301-308 (2003)

Vlaisavljevic *et al., Reproductive BioMedicine Online* 7:301-308 (2003; hereafter Vlaisavljevic) confirms that programming using LHRH antagonists in conjunction with oral contraceptives is practicable for restarting the menstrual cycle for purposes of programming COS/ART procedures as set forth in the claimed invention (See Appendix B). Specifically, Vlaisavljevic compared the effectiveness of a flexible single dose LHRH antagonist with a single dose LHRH agonist to an ovarian stimulation treatment cycle. For each treatment group, the patients took oral contraceptives during the initial days of their menstrual cycle to properly program ovarian stimulation between Monday and Friday. Vlaisavljevic concluded that "using the antagonists in ovarian stimulation, oestrogen deprivation symptoms associated with agonist-induced down-regulation can be avoided, but at the same time the cetrorelix protocol, in combination with oral contraceptive synchronization, provides the same flexibility in programming the cycle." (See, page 307, 1st column, last 5 lines).

Fanchin *et al., Human Reproduction* 18:2698-2703 (2003)

Fanchin *et al., Human Reproduction* 18:3698-2703 (2003; hereafter Fanchin) confirms that programming LHRH antagonist COS/ART cycles is practicable by intake of

oral estradiol as set forth as an alternative in the claimed invention (See Appendix C). Fanchin teaches administering oral estradiol during the luteal phase to reduce the concentrations of endogenous follicle stimulating hormone and prevent early follicular growth. After estradiol was discontinued, ovarian stimulation protocols were started under a programmed regimen. (See page 2699, 2nd column). Fanchin concluded that luteal estradiol administration increases the number of follicles reaching maturation at once and potentially improves results of ovarian stimulation therapy. (See page 2702, 2nd column) Again, Fanchi, like Vlaisavljevic, verifies the teachings of our application regarding the novel and unexpected results of improving female fertility by resetting the menstrual cycle for predictable programming of the COS/ART procedures.

Naether et al., 6th International Symposium on GnRH Analogus in Cancer and Human Reproduction, Geneva, Switzerland (2001)

Naether *et al.*, 6th International Symposium on GnRH Analogus in Cancer and Human Reproduction, Geneva, Switzerland (2001; hereafter Naether) was the first to report the use of LHRH in woman whose cycles were programmed with oral monophasic contraceptives administered in the pre-treatment cycle prior to ovarian stimulation (See Appendix D). The investigators concluded that cetrorelix treatments for LH surges were not adversely affected by using programmed COS/ART procedures where oral contraceptives where given to start a new menstrual cycle. The cited prior art in the examiner's obvious rejection simply teaches using LHRH antagonists to prevent LH surges in non-programmed COS/ART procedures. Thus, the applicants respectfully submit that this abstract confirms the findings that programming the COS/ART procedures by intake of oral contraceptives is an unexpected results as set forth in the claimed invention from the teachings of the prior art.

A. Obruca, European Society for Human Reproduction and Embryology, Lausanne (2001)

A. Obruca, European Society for Human Reproduction and Embryology, Lausanne (2001; hereafter Obruca) reported the results of a randomized controlled study to evaluate the use of oral contraceptive pretreatments to ensure that ovarian stimulation could begin on a desired day to better schedule oocyte retrieval (Appendix D). Specifically, one group of patients underwent the classic GnRH antagonist protocol where oral contraceptives where given for 18-28 days and the final tablet was taken on a Sunday. The following Friday, ovarian stimulation was started. In terms of oocyte retrieval, there was no weekend pick ups in the oral contraceptive pretreatment group compared with a small number of weekend pick

up groups in the classic protocol groups (as taught in the combined seven references cited the examiner in the obviousness rejection). The investigator concluded that the "oral contraceptive group showed better scheduling of the start of the cycle and of oocyte retrieval, as well as a reduction of functional cysts prior to stimulation." Again, Obruca confirms our findings that intake of oral contraceptives unexpectedly allows physicians to program LHRH antagonist COS/ART procedures to optimize oocyte release and fertilization between Mondays and Fridays.

In view of the foregoing amendment and remarks, the applicants respectfully request that the rejection of claims 1 and 3-24 under 35 U.S.C. §103(a) as allegedly being obvious over Engel, Albano, Felberbaum, and Garfield in view of Deghenghi, Rabasseda, and Kent, has been overcome and should be withdrawn.

Rejection Pursuant to the Judicially Created Doctrine of Obviousness Double Patenting

On pages 15 and 16 of the official action, the examiner rejected claims 1 and 3-24 under the judicially created doctrine of obviousness double patenting over claims 1-6 of U.S. Patent No. 6,319,192 (hereafter the '192 patent). The examiner alleged that the claims of the instant application (*i.e.*, claims drawn to the method of therapeutic management of infertility by programming COS/ART procedures) are not patentably distinct from the claimed methods of the '192 patent. Specifically, the examiner asserted that the '192 patent is directed to a method of therapeutic management of infertility by intrauterine insemination consisting of substantially similar method steps and administering the same pharmaceutical agents as LHRH antagonists, such as cetrorelix, HCG, native LHRH, LHRH agonists, and recombinant LH.

In view of the foregoing amendment to claim 1, the applicants respectfully submit that the novel step of resetting the menstrual cycle using progesterone only, or progestogen or progestogen plus oral contraceptives in combination with LHRH antagonists during the luteal phase and early stages of the follicular stage to reset the menstrual cycle is patentably distinct over the claimed methods of the '192 patent. Nowhere in the disclosure of the '192 patent or the claimed invention is there a teaching or suggestion regarding the importance of programming the COS/ART procedures by resetting the menstrual cycle using progestogen or other oral conceptive preparations. This novel finding allows physicians to optimize the controlled stimulation of the ovaries and fertilize the eggs using assisted reproductive techniques. As discussed above, claim 3 has been canceled without prejudice. Accordingly,

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the applicants respectfully submit that in view of the foregoing amendment to claim 1 (and its dependent claims 3-24), the rejection of claims 1 and 3-24 under the judicially created doctrine of obviousness double patenting as been overcome and should be withdrawn.

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CONCLUSION

In view of the foregoing, the claims are now believed to be in form of allowance, and such action is hereby solicited. If any point remains at issue which the examiner feels may be best resolved through a personal or telephone interview, please contact the undersigned at the telephone number below.

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